JCCC Honors Journal

Volume 9
Issue 2 *Spring 2018*

Article 4

2018

Fetal Programming: How Intrauterine Environmental Factors Influence Health and Disease

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Abstract
How Intrauterine Environmental Factors Influence Health and Disease

Once thought of as inconsequential, the prenatal period has recently acquired some awareness as being a sensitive time during which environmental factors can modulate gene expression as well as regulate fetal growth and development. The prenatal period encompasses the genesis of an embryo, the intricate process of fetal maturation, concludes with the birth of the infant, and is marked by the profound influence it exerts on long-term health trajectories. The notion that intrauterine environmental factors can reset physiological parameters "and the resetting can endure into adulthood and even affect the following generation" is known as "fetal programming" (Agin, 2010, p. 6 -7). This is a fairly new concept that offers encouraging insight into the origins of some of the most prevalent ailments that affect the population. Numerous research studies have demonstrated the correlation between maternal circumstances and fetal consequences; some of which include prenatal stress with mental health disorders, maternal body mass index with cardiovascular disease, and under or over nutrition with metabolic disorders. Thus, the fetal programming paradigm provides the opportunity to take preventative measures against the known factors to ensure a more favorable health outcome for future generations; however, in order to gain a better understanding of the complex biological mechanisms underlying the fetal programming concept, more applied research needs to be conducted.

Cover Page Footnote
The faculty mentor for this Honors project was Professor Nanette Lanier, Nursing.

Once thought of as inconsequential, the prenatal period has recently acquired some awareness as being a sensitive time during which environmental factors can modulate gene expression as well as regulate fetal growth and development. The prenatal period encompasses the genesis of an embryo, the intricate process of fetal maturation, concludes with the birth of the infant, and is marked by the profound influence it exerts on long-term health trajectories. The notion that intrauterine environmental factors can reset physiological parameters "and the resetting can endure into adulthood and even affect the following generation" is known as "fetal programming" (Agin, 2010, p. 6 -7). This is a fairly new concept that offers encouraging insight into the origins of some of the most prevalent ailments that affect the population. Numerous research studies have demonstrated the correlation between maternal circumstances and fetal consequences; some of which include prenatal stress with mental health disorders, maternal body mass index with cardiovascular disease, and under or over nutrition with metabolic disorders. Thus, the fetal programming paradigm provides the opportunity to take preventative measures against the known factors to ensure a more favorable health outcome for future generations; however, in order to gain a better understanding of the complex biological mechanisms underlying the fetal programming concept, more applied research needs to be conducted.

Although transient in its existence, the placenta is conceivably the single most important organ of the body; however, it may also be the least understood. Ricci, Kyle, and Carman (2016) suggest that the placenta serves as the interface between the mother and the growing fetus, connected via the umbilical cord that serves as a conduit, supplying the fetus with essential nutrients and oxygen (p. 342). Recently, the view that the placenta was merely a "static plug" that connected the mother to the developing fetus, has begun to change, attributable to the recent advancements in molecular and imaging technologies (Konkel, 2016, p. 1). These advancements

have prompted the discovery that the placenta "also functions as a neuroendocrine organ that produces hormones and other important molecules to spur fetal growth and development [and that the] placenta, in essence, may be the master regulator of the fetal environment" (Konkel, 2016, p. 2). Consequently, this vital maternal-fetal connection can also adversely impact the life of the child by way of transference of growth-inhibiting maternal glucocorticoids, such as cortisol, as well as environmental toxins, which can facilitate the development of "a range of cognitive and emotional disorders, particularly depressive, anxiety and attention related mental health conditions" (Lewis et al., 2015, p. 1217). Furthermore, this essential organ plays an integral role in what experts call the "developmental origins of health and disease" (Konkel, 2016, p. 1).

During the bitterly cold winter of 1944 when Germany occupied the Netherlands, a Dutch railroad strike spurred the Nazis to cease food shipments to the densely populated western region of the country. This resulted in mass starvation, with food rations as little as 400 to 800 calories per day. This famine, known as the Dutch Hunger Winter, although devastating, provided the scientific and medical communities with a wealth of knowledge related to the developmental origins of health and disease. According to author and scientist, Dan Agin (2010), this knowledge was attainable due to the accessibility of "long-term follow-up . . . of mothers who had experienced malnutrition in [the] first, second, or third trimester [of pregnancy]" (p. 86). It was reported that babies whose mothers were nutritionally deprived during the first trimester of gestation "experienced elevated rates of obesity, altered lipid profiles, and cardiovascular disease" (Schultz, 2010 p. 16757). Furthermore, "among the findings was an increase in the prevalence of schizophrenia and other mental illness among the offspring in gestation during the famine" (Agin, 2010, p. 86). As discussed by Schultz (2010), this is likely related to the

development of the central nervous system structures occurring early in gestation (p. 16757), which is a formative time of the prenatal period. Ultimately, the Dutch Hunger Winter contributed to the mounting evidence for the fetal programming phenomenon.

In his cogent exposé, *More than Genes*, Dan Agin (2010) proposes that there are certain environmental factors that can disrupt the development of the fetus in utero, which can have a significant impact on the future health of the child (p. 98). Among the maternal environmental factors are placental insufficiency and hypoxia; nutrition; temperature changes; maternal infection and inflammation; glucocorticoids; and exposure to toxins. Placental insufficiency, a condition resulting from decreased blood flow and placental perfusion, can cause intrauterine growth restriction of the fetus or a "small for gestational age" infant. Additionally, babies born with intrauterine growth restriction have an increased risk for neurological problems (p. 98-99). Placental insufficiency leads to fetal hypoxia, which involves depriving the fetus of an essential component for growth and development. Hypoxia is associated with low birth weight and can have deleterious consequences, such as damage to the developing central nervous system, including the death of neurons and diminished growth of neural axons and dendrites (p. 100). Another fundamental component of fetal growth and development that can be altered by maternal circumstance is nutrition. Agin states (2010), "[i]nadequate fatty acid nutrition during fetal growth affects the chemistry of nerve cell membranes and can disrupt the migration of neurons in the fetal brain" (p. 99). Furthermore, an elevated maternal temperature and a subsequent elevated fetal temperature can result in a slew of medical abnormalities, such as intellectual disabilities, physical defects, and cardiac anomalies (p. 100). Maternal infection and inflammation usually occur concurrently, and both can cause fetal brain damage (p. 100-101). Moreover, exposing the fetus to glucocorticoids, such as cortisol, increases the risk ". . . of later

development of hypertension, diabetes, and psychiatric disorders, such as depression and anxiety" (p. 101). Finally, exposure to toxins, including cigarette smoking and use of cocaine, alcohol, and pharmaceutical substances puts the fetus at risk for long-term health issues (p. 102 – 103).

To better understand the concept of fetal programming, it is important to discuss the significance of epigenetic inheritance and its components as well as its implication in the origins of health and disease. Babenko, Kovalchuk, and Metz (2014) define epigenetics as "the study of heritable changes in the gene expression profile of a cell that are not caused by changes in the nucleotide sequence of the DNA" (p. 71). Furthermore, the components that play a role in this process of phenotypic inheritance are DNA methylation, non-coding RNA-mediated modifications, histone modification, and chromatin remodeling (Babenko et al., 2014, p. 71). However, according to Babenko et al., DNA methylation; a mechanism that occurs by the addition of a methyl group to a DNA molecule causing modification of the function of the genes, which in turn influences the gene expression; has been extensively studied and is the most established component (2014, p. 71).

Babenko et al. (2014) found that the highly studied epigenetic mark, DNA methylation:

> plays a critical role during mammalian development . . . has a variety of functions and is required for several processes, such as silencing of transposable elements and pericentromeric repeats to ensure genome integrity, inactivation of X-chromosomes, and genomic imprinting. (p.77)

Multiple experiments using mice have been conducted linking alterations in DNA methylation and neuronal impairment. Additionally, human studies show that various mutations in the enzymes necessary for the transfer of a methyl group to DNA can cause "neurodegeneration in

the form of hereditary sensory neuropathy with dementia and hearing loss . . . [and] neurodevelopmental disorders, including severe neonatal encephalopathy, X-linked mental retardation, autism, and Rett syndrome" (Babenko et al., 2014, p. 78). Moreover, Babenko et al. (2014) suggest that when there are alterations in the DNA methylation machinery the placental development is compromised and can result in low birth weight infants and various pregnancy complications, which can adversely affect fetal brain development (p. 78).

Recent research has provided valuable insight into the complex relationship between stress and fetal programming. Specifically, maternal stress experienced during pregnancy when the fetus is vulnerable to environmental factors. As stated by Babenko et al. (2014), "[s]tress initiates a cascade of biochemical reactions in the body and, depending on its duration and severity, may represent a risk factor for a variety of health complications, including neurological and mental illnesses" (p. 79). Although stress is an innate and beneficial response in the short term, it can develop into a pathological condition. In response to stress, hormones are secreted by the hypothalamus, which in turn activates the pituitary gland to secrete a hormone that prompts the adrenal glands to release glucocorticoids, such as cortisol, into the bloodstream. This stress response system is called the HPA axis and with frequent activation of this system, damage to the developing central nervous system can result. Moreover, experiencing stress during a critical time period for fetal growth and development can have long-term consequences related to the brain's hormonal response (Babenko et al., 2014, p. 79 - 80). According to Agin (2010), "there's enough evidence that makes biological sense to underscore the importance of maternal stress as a mediating variable between the maternal psychological and social environment and the development of the fetal body and brain" (p. 282).

Although the science is fairly new, there have been numerous promising epigenetic studies that mediate the connection between intrauterine stress exposure and the future mental health outcomes of the child. In Lewis et al.'s (2015) research on maternal psychological health and fetal programming, they reported that the many "metabolic and functional changes" that coexist with maternal mental distress can impact fetal development by way of impairing transport of oxygen and glucose to the fetus, disrupting endocrine function, promoting fetal oxidative stress, and a decrease in the amount of circulating insulin-like growth factors that directly control development and growth of a fetus (p. 1218). With maternal psychological distress and a subsequent increase in maternal stress hormones, such as cortisol and adrenaline, there is a possibility of transference to the fetus via the placenta (Lewis et al., 2015, p. 1218). Additionally, there have been findings to support the notion that "[e]arly exposure of offspring to maternal anxiety and depression has been associated with vulnerability to behavioural and emotional problems during childhood and adolescence," including attention-deficit/ hyperactivity disorder and delayed language development (Lewis et al., 2015, p. 1219). Moreover, Agin (2010) examined the effects of natural disasters, which are extremely stressful events, on fetal development. Interestingly, he found that twenty-three years after a massive earthquake in China that killed hundreds of thousands of people, those that were in fetal development at the time of the disaster showed alterations "in intellectual functioning, depression, and the size of certain brain regions" (p. 284). Another factor related to maternal stress that should be considered is its association with reduced fetal birth weight, which according to David Barker, an epidemiologist, is "correlated with [future] coronary artery disease, hypertension, stroke, and type 2 diabetes" (Agin, 2010, p. 87).

Relatedly, adverse fetal environments have been reported to be associated with an increased risk of developing schizophrenia, a serious mental ailment. According to Videbeck (2017), “schizophrenia causes distorted and bizarre thoughts, perceptions, emotions, movements, and behavior. It cannot be defined as a single illness; rather, schizophrenia is thought of as a syndrome or as a disease process” (p. 266). Several epidemiological studies support the fetal programming hypothesis in that schizophrenia can be linked back to maternal environmental factors, both exogenous and endogenous, that disrupt fetal development. These prenatal factors include teratogens, nutrition, infection, stress, and paternal age (Debnarth, Venkatasubramanian, Beck, 2014, p. 92 – 94). Debnarth et al. (2014) reported that neurotoxic substances, from industrial chemicals to recreational illicit drugs to over the counter analgesics, can influence fetal brain development and enhance the risk of schizophrenia (p. 92). Another important factor that plays a role in schizophrenia pathogenesis is maternal nutrition. As evidenced by the Dutch Hunger Winter, “prenatal malnutrition leads to long-term brain impairment and increased risk of schizophrenia” (p. 93). Likewise, eating a poor-quality diet, rather than simply not consuming enough food, can have the same deleterious effects. Moreover, there is mounting evidence that suggests the relationship between prenatal infection and the etiology of schizophrenia. Such infections include influenza, rubella, herpes simplex virus, and cytomegalovirus (Debnarth et al., 2014, p. 93). As previously discussed, maternal stress can alter fetal brain development via programming of the HPA axis. Finally, studies have shown an association with “advanced paternal age” and developing schizophrenia later in life (p. 94).

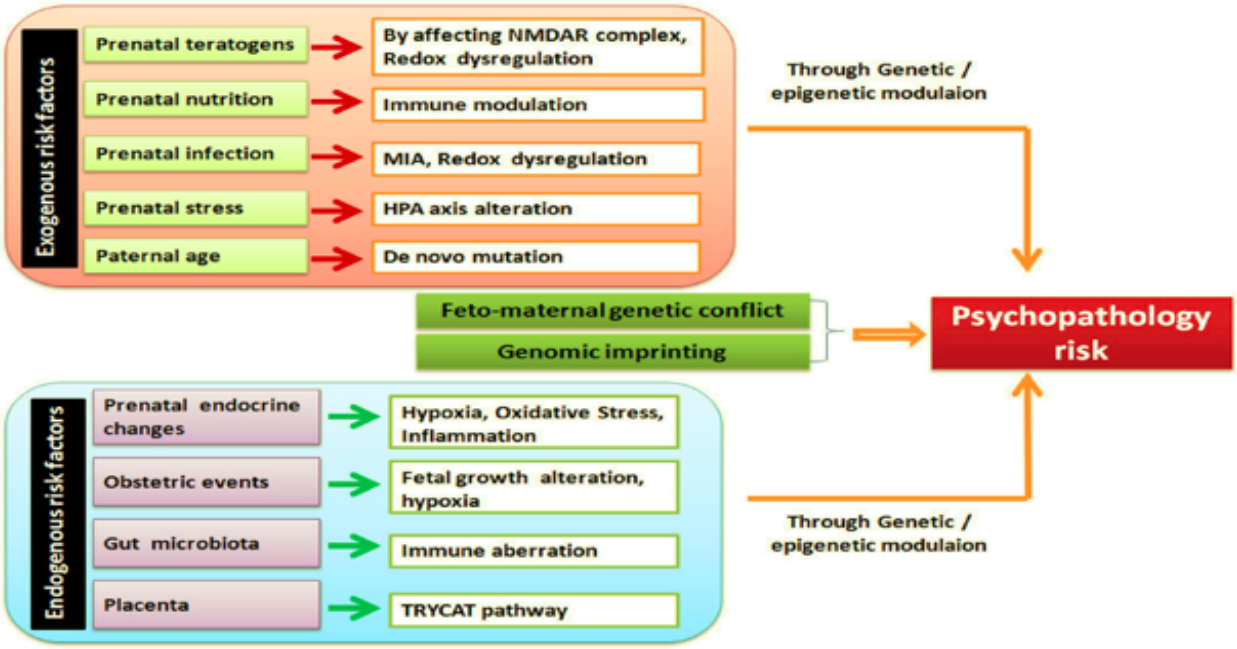

Figure 1. Summary of potential prenatal endogenous and exogenous risk factors and/or mechanisms leading to psychopathology. Adapted from "Fetal Programming of Schizophrenia: Select Mechanisms," by M. Debnarth, G. Venkatasubramanian, and M. Berk, 2014, *Neuroscience and Biobehavioral Reviews*, *49*, p. 96. Copyright 2014 by Elsevier Ltd.

With the increasing prevalence of obesity worldwide, recent research efforts have been focused on the etiology and concept of "obesity programming" (Freeman, 2010, p. 113). In other words, intrauterine environmental factors that can program pathways in the fetus that can lead to obesity later in life. The emergence of this concept occurred in the 1980s when David Barker linked low birth weight infants with adverse health outcomes such as obesity, cardiovascular disease, and metabolic dysfunction disorders. Freeman (2010) states that "[Barker's] hypothesis suggests that poor nutrition in fetal life can lead to permanent changes in the glucose-insulin axis" and among these changes include dysfunction of the pancreatic beta cells that release insulin (p. 114). This impairment of insulin secretion is an appropriate compensatory mechanism

when there is an inadequate nutrient intake; however, when there is an abundance of food available this leads to "insulin resistance, obesity, metabolic syndrome and type 2 diabetes later in life" (Freeman, 2010, p. 114). In their neuroendocrinology review article, Dearden and Ozanne (2015), conversely suggest that early life origins of obesity and metabolic disease can derive from maternal obesity (p. 4). Dearden et al. (2015) also highlighted a study that revealed a decreased incidence of obesity, insulin resistance, and hypertension in babies born to mothers who underwent bariatric surgery to induce weight loss before becoming pregnant as compared to their older siblings (p. 4). Although there is compelling evidence to suggest the relationship between environmental factors during gestation and future metabolic and vascular disease, further research is needed to definitively identify the mechanisms that play a role in fetal programming.

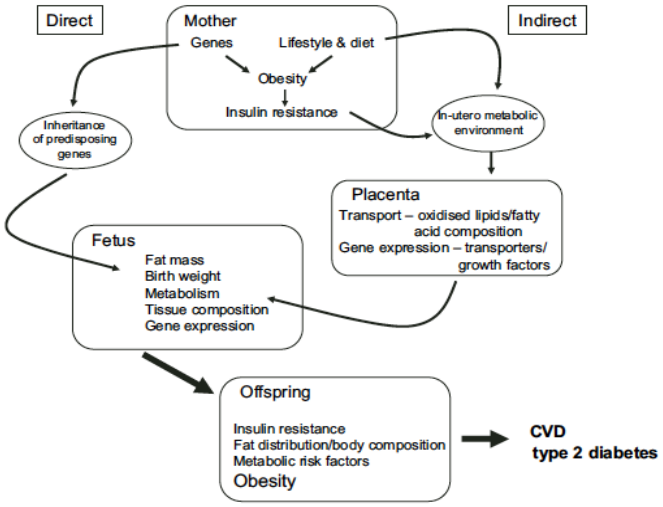

Figure 2. Programming of offspring obesity. Fetal body composition, metabolism and gene expression may be influenced by the mother to develop patterns resulting in future obesity. Adapted from "Effects of Maternal Obesity on Fetal Growth and Body Composition: Implications for Programming and Future Health," by D. Freeman, 2009, *Seminars in Fetal & Neonatal Medicine, 15,* p. 116. Copyright 2009 by Elsevier Ltd.

Fetal programming can lead to transgenerational epigenetic inheritance, meaning unfavorable intrauterine environmental factors that affect the fetus's future health and disease outcomes can also potentially negatively influence subsequent generations' health trajectories. To put an end to this vicious cycle, recognition of these factors and interventions to minimize their impact are crucial, and nurses play a key role in this process. Whether in the pre-pregnancy stage or during pregnancy, providing education to potential mothers is vitally important. For example, suggesting lifestyle changes, such as a consuming a nutrient dense diet and implementing moderate exercise, can positively impact the fetus's future health as well as break the cycle of obesity and metabolic disease (Dearden and Ozanne, 2015, p. 12). Furthermore, explaining that the nine months of gestation is the most vulnerable and malleable period for fetal growth and development, thus avoidance of toxic substances and utilization of appropriate stress reduction techniques is of the utmost importance. Additionally, Dearden and Ozanne (2015) suggest that women are more susceptible to employ healthy lifestyle changes when they are pregnant as to "improve their own health for the benefit of their unborn child" (p. 12).

It is well established that life in utero is a time marked by great fragility with instances of maternal-fetal opposition, not merely a time of congruous union of mother and baby. The knowledge that certain prenatal factors disrupt the growth and development of the fetus, which in turn can have undesirable, long-term health implications, provides an opportunity to preclude such an outcome and ultimately eliminate the avoidable fetal impacts altogether. There is still much to ascertain about the exact mechanisms that play a role in the link between intrauterine environmental factors and the development of adverse health outcomes; however, the science and medical communities have laid a solid foundation for future researchers to build upon.

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